(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 October 2004 (21.10.2004)

PCT

(10) International Publication Number
WO 2004/089302 A3

(51) International Patent Classification[7]: C12Q 1/68, C07K 14/47, C12N 5/06

(21) International Application Number: PCT/US2004/010582

(22) International Filing Date: 5 April 2004 (05.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/460,526	3 April 2003 (03.04.2003)	US
60/475,825	3 June 2003 (03.06.2003)	US
PCT/US04/06308	2 March 2004 (02.03.2004)	US

(71) Applicant *(for all designated States except US)*: **PROTEOLOGICS, INC.** [US/US]; 40 Ramland Road South, Suite 10, Orangeburg, NY 10962 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **YAAR, Liora** [IL/IL]; 8 Kalisher Street, 43354 Raanana (IL). **ALROY, Iris** [IL/IL]; Hashirion Street 10/17 (IL). **REISS, Yuval** [IL/IL]; Hahavazelet 11/6, Kiriat-Ono (IL). **TAGLICHT, Daniel, N.** [IL/IL]; 33 Ha'Alonim St., Lapid 73133 (IL).

(74) Agents: **VARMA, Anita** et al.; Ropes & Gray LLP, One International Place, Boston, MA 02110-2624 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 29 September 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: POSH POLYPEPTIDES, COMPLEXES AND RELATED METHODS

(57) Abstract: The application provides novel complexes of POSH polypeptides and POSH-associated proteins. The application also provides methods and compositions for treating POSH-associated diseases such as neurological disorders.

WO 2004/089302 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/10582

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/68, C07K 14/47,C12N 5/06
US CL : 435/5, 69.9, 199
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/5, 69.9, 199

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, STN, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Tapon et al. A new Rac target POSH is an SH3-containingscaffold protein involved in the JNK and NF-kappaB signalling pathways, EMBO Journal Vol. 17 N0.5, pp. 1395-1404.	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2005 (29.04.2005)	23 AUG 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Valerie Bell-Harris Arthamurthy Ponnathapura Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/10582

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/10582

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I- Claims 1 and 2 are drawn to an isolated purified or recombinant complex comprising POSH and POSH-AP wherein the POSH-AP is HERPUD1.
Group II- Claims 3 and 4 are drawn to an isolated purified or recombinant complex comprising POSH and ubiquitinated POSH_AP wherein the ubiquitinated POSH-AP is HERPUD1.
Group III- Claims 5 and 6 are drawn to purified ubiquitinated HERPUD1.
Group IV- Claims 7, 8 and 9 are drawn to a method of identifying or evaluating an agent that modulates a HERPUD1 function.
Group V - Claims 10 and 11 are drawn to a method of inhibiting an activity of POSH-AP in a cell.
Group VI- Claims 12-15 a method of identifying a modulator of POSH wherein a modulator is tested for its ability to ubiquitinate a second substrate.
Group VII- Claims 16 -19 are drawn to a method of identifying an agent that inhibits a neurological disorder by POSH ubiquitination.
Group VIII- Claims 20-27 and 28 in part are drawn to a method of treating a neurological disorder by inhibiting ubiquitine ligase activity of POSH on HERPUD1 using siRNA or an anti-sense construct.
Group IX- Claims 20-27 and 28, 29 in part are drawn to a method of treating a neurological disorder by inhibiting ubiquitine ligase activity of POSH on HERPUD1 using small molecules.
Group X- Claims 20-27 and 28 in part are drawn to a method of treating a neurological disorder by inhibiting ubiquitine ligase activity of POSH on HERPUD1 using an antibody.
Group XI- Claims 30 and 31 are drawn to a method of identifying an agent to treat a neurogical disorder by identifying an agent that disrups a complex between a POSH-POSH-AP.
Group XII- Claims 32-34 are drawn to a method of inhibiting the progression of a neurological disorder by an agent that inhibits POSH-POSH-AP interaction.
Group XIII- Claims 35, 39, 40 in part and claims 36 and 37 are drawn to a method of testing an agent for use in treatment of a neurological disorder comprising contacting cells that produce amyloid polypeptide with siRNA that inhibits POSH activity or expression and evaluating the effect of the agent on apoptosis of the cells..
Group XIV- Claims 35, 39, 40 in part and claims 36 and 37 are drawn to a method of testing an agent for use in treatment of a neurological disorder comprising contacting cells that produce amyloid polypeptide with a small molecule that inhibits POSH activity or expression and evaluating the effect of the agent on apoptosis of the cells..
Group XV- Claims 35, 39, 40 in part and claims 36 and 37 are drawn to a method of testing an agent for use in treatment of a neurological disorder comprising contacting cells that produce amyloid polypeptide with an antibody that inhibits POSH activity or expression and evaluating the effect of the agent on apoptosis of the cells.

The inventions listed as Groups I-XV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking the inventions of group I-XV is the use of a POSH polypeptide and/or a POSH-AP complex in identifying agents that modulate POSH interaction or ubiquitination, and various methods such as a method of identifying an agent(s) that inhibits a neurological disorder, treating a neurological disorder with an agent that inhibits the ubiquitine ligase activity of POSH, inhibiting the progression of neurological disorders, testing an agent on apoptosis in cells. However Tapon et al., 1998 teach that POSH is expressed in the brain and acts as a scaffold proteinthat contributes in Rac1-dependent signaling functions, including promotion of apoptotic cell death. Tapon et al.,

identified POSH as a Rac interacting protein, triggers cell death and stimulates the JNK pathway that Rac specifically interacts with POSH.